Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1348845

*J Med Palliat Care*. 2023;4(5):516-523

# Systemic immune inflammation indices: novel predictors for preterm premature rupture of membranes and associated complications

Gökçe Naz Küçükbaş, Arzu Yavuz

Department of Obstetrics and Gynecology, Kocaeli City Hospital, Kocaeli, Turkey

**Cite this article as**: Küçükbaş GN, Yavuz A. Systemic immune inflammation indices: novel predictors for preterm premature rupture of membranes and associated complications. *J Med Palliat Care*. 2023;4(5):516-523.

**Received**: 23.08.2023 ◆ **Accepted**: 29.09.2023 ◆ **Published**: 27.10.2023

## ABSTRACT

**Aims**: This study aimed to investigate the relationship between systemic immune inflammation (SII) and response indices (SIRI), which are new markers of systemic inflammation derived from immune cells, and preterm premature rupture of membranes (PPROM), as well as adverse pregnancy outcomes.

**Methods**: The retrospective study included 75 women with singleton pregnancies complicated by PPROM between the 24th and 34th gestational week and 75 healthy pregnant women who delivered at term without any additional diseases (control group). Inflammation indices were calculated based on neutrophil (N), platelet (P), lymphocyte (L), and monocyte (M) counts as follows: The neutrophil-to-lymphocyte ratio (NLR)=N/L; the platelet-to-lymphocyte ratio (PLR)=P/L; SII=(N×P)/L; and SIRI=(N×M)/L.

**Results**: The median NLR (4.8 vs. 3.5, p <0.001), median PLR (145.1 vs. 126.5, p<0.001), median SII (1208.6 vs. 807.4, p<0.001), and median SIRI (3.1 vs. 2.0, p<0.001) were higher in the PPROM group compared to the control group. Multiple logistic regression analysis showed that increased SIRI (OR= 7.05, p=0.010), as well as increased C-reactive protein levels were determined as independent predictors of PPROM. In the PPROM group, the SIRI was higher in the presence of combined complications compared to without complications (3.4 vs. 2.5, p<0.001). The SIRI showed superior diagnostic performance in predicting the presence and complications of PPROM compared to other inflammation indices.

**Conclusion**: The PPROM group had higher leukocyte-based inflammation indices compared to the control group. Due to the superior diagnostic performance of the SIRI in distinguishing both PPROM and combined complications compared to other leukocyte-based inflammation indices, it may serve as a significant screening tool for PPROM.

**Keywords**: Preterm premature rupture of membranes, immune inflammation index, pregnancy complications, neonatal outcomes

## INTRODUCTION

Preterm premature rupture of membranes (PPROM) is defined as the rupture of the membranes prior to 37 weeks of gestation, occurring without any initiation of labor.[1] It complicates about 3% of pregnancies and heightens the risk of chorioamnionitis, placental abruption, preterm birth, and neonatal challenges such as respiratory distress syndrome, necrotizing enterocolitis, and intraventricular hemorrhage.[2] Although the exact pathophysiological mechanism of PPROM has not been clearly defined, it is widely recognized that inflammation plays a significant role in the rupture of fetal membranes.[3] This is consistent with the inclusion of antibiotic administration in the clinical management of PPROM.[4]

It has been established that PPROM can occur with intra-amniotic infection (detectable microorganisms along with high interleukin-6 (IL-6) concentrations in the amniotic fluid), sterile intra-amniotic inflammation (high IL-6 concentrations without detectable microorganisms), or without intra-amniotic inflammation (low IL-6 concentrations).[5] On the other hand, changes in enzymes such as tropoelastins, elastin cross-linking enzymes, lysyl oxidase, and lysyl oxidase-like enzymes, which are involved in the amniotic extracellular matrix and contribute to the mechanical function of the amnion, could make the membrane more prone to early rupture.[6] Additionally, the intrauterine environment undergoes redox changes during pregnancy. Imbalanced redox changes can lead to the accumulation of reactive oxygen species (ROS), and an excessive release of cytokines, chemokines, growth factors, and matrix metalloproteases (MMPs).[7] For these reasons, the inflammatory response triggered by the immune system may play a significant role in the development of PPROM.

**Corresponding Author**: Gökçe Naz Küçükbaş, nazkuc@gmail.com

This work is licensed under a Creative Commons Attribution 4.0 International License.

PPROM, characterized by infection and inflammation, can lead to an excessive release of immune cells.[8] Leukocytes and their subtypes obtained from a complete blood count serve as the first line of defense in an inflammatory milieu.[9] In this context, several studies have reported a significant relationship between various inflammatory markers and PPROM.[10-14] However, biomarkers involving more comprehensive immune cells may enhance the predictive ability of PPROM.

In the landscape of modern medicine, the search for comprehensive and reliable biomarkers to gauge individuals' overall health and prognostic potential has become increasingly important.[15,16] Within this realm, systemic immune inflammation (SII) and response (SIRI) indices have emerged as promising candidates for providing deeper insights into the functioning of the immune system and their potential implications across various medical conditions.[17,18] The SII, which is an indicator of inflammatory status, is calculated by platelet count × neutrophil count/lymphocyte count,[19] while the SIRI, which is an indicator of the balance between the inflammatory response and immune status, is calculated by neutrophil count × monocyte count/lymphocyte count.[20] These indices are reported to have significant diagnostic performance in various diseases.[17-22] However, the diagnostic performance of these indices regarding PPROM or adverse pregnancy outcomes has not yet been sufficiently investigated.

We hypothesized that there might be an association between leukocyte-based inflammatory indices and PPROM. Thus, this study aimed to investigate the relationship SII and SIRI indices, which are new markers of systemic inflammation derived from immune cells, and PPROM, as well as adverse pregnancy outcomes.

## METHODS

Following the principles set forth in the Declaration of Helsinki, this retrospective study was conducted at the Kocaeli Derince Training and Reseach Hospital Gynecology Clinic between January 2022 and December 2022. The study was carried out with the permission of Kocaeli Derince Training and Reseach Hospital Clinical Researches Ethics Committee (Date: 12.01.2023, Decision No: 2023-001). The local ethics committee waived the requirement of informed consent due to the retrospective nature of the research.

### Study Population

A total of 256 women with singleton pregnancies complicated by PPROM between the 24th and 34th gestational week were evaluated retrospectively. The exclusion criteria were multiple pregnancy, smoking or substance abuse, maternal infection (positive cultures of urine, blood, throat swab and cervical swab), fetal infection (positive maternal serum tests indicating acute intrauterine infection test results of toxoplasmosis, cytomegalovirus, rubella or any other microorganism such as anti- cytomegalovirus immunoglobulin-M), gestational or pregestational diabetes mellitus, all types of hypertensive diseases of pregnancy, hematologic or autoimmune diseases, malignancies, poor nutritional status (body mass index <18.5 kg/m2),[23] being on any medication except antenatal supplements, history of invasive procedure or surgery during pregnancy, insufficient cervix, and antenatal trauma. Women with pregnancies complicated with PPROM but who received any treatment of antenatal corticosteroids, magnesium, or antibiotherapy before admission were also excluded. After this exclusion process, 70 women with singleton pregnancies complicated with PPROM between the 24$^{th}$ and 34$^{th}$ gestational week were enrolled in this study. The control group was comprised of pregnant women who delivered at term without any additional diseases and were matched 1:1 in terms of gestational age with the PPROM group.

### Study Protocol

PPROM was diagnosed under sterile speculum examination either with the visualization of amniotic leakage from the cervix or with the detection of an amniotic protein called insulin-like growth factor binding protein in the posterior fornix (Amni Sure, QIAGEN, Germantown, USA) complying with the guidelines.[1] After PPROM diagnosis, the pregnant women were admitted to the hospital. After the first blood sample for this study was drawn, a single course of antenatal corticosteroids and antibiotic prophlaxis were administered. Upon admission, 1 gram of azithromycin, orally, and 2 grams of ampicillin, intravenously, were administered every 6 h for the first 2 days, followed by 500 mg of amoxicillin, orally, every 8 h for an additional 5 days. This prophylaxis complied with the ACOG Guidelines.[24] Delivery was planned at the 34$^{th}$ week of gestational age unless chorioamnionitis, placental abruption, or fetal distress were present.[1] From hospitalization to delivery, the physical and laboratory signs and findings of chorioamnionitis, placental abruption, or fetal distress were investigated.

The demographic and clinical data, such as maternal age, gravida, parity, abortus, gestational week at amniorrhexis, number of days until delivery, delivery mode, birth weight, gender, examination findings, PPROM complications, need for neonatal intensive care unit (NICU) admission, and days of stay were extracted from the electronic records of the patients. Infants were stratified according to their birth weight into the following categories: those weighing 2500 grams or more were classified as having a normal birth weight, those below 2500 grams as low birth weight, those below 1500 grams as very low birth weight, and those under 1000 grams as extremely low

birth weight. Infants with a gestational age of 37 weeks and above were categorized as term, those between 34-37 weeks as late preterm, those between 32-34 weeks as moderate preterm, those between 28-32 weeks as very preterm, and those below 28 weeks as extremely preterm.[25] Blood samples of all patients were taken at admission. All samples were analyzed in a single laboratory using the same methodology as described below.

### Laboratory Parameters

A Sysmex XN-1000 hematology analyzer (Sysmex USA, Inc. Lincolnshire, IL, USA) was used to evaluate the venous blood samples of the patients. The levels of hemoglobin (photometrically) and C-reactive protein (CRP) (immunoturbidimetric method), and the platelet count (impedance method) were determined. The urine culture test was also used to determine urinary infection diseases.

The inflammation indices were respectively calculated as follows: The neutrophil-to-lymphocyte ratio (NLR)=neutrophil count/lymphocyte count, platelet-to-lymphocyte ratio (PLR)=platelet count/lymphocyte count, SII=(platelet count × neutrophil count)/lymphocyte count, and SIRI=(neutrophil count × monocyte count)/lymphocyte count.[19,20]

### Statistical Analysis

All of the data were analyzed with IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA). Numerical data determined to be normally distributed based on the results of the Kolmogorov-Smirnov test were given as the mean±standard deviation (SD), while non-normally distributed variables were given as the median ($25^{th}$-$75^{th}$ quartile). For the comparison of numerical data between the control and PPROM groups, data exhibiting a normal distribution was analyzed using the Student's T-test, whereas data without a normal distribution was analyzed with the Mann-Whitney U test. The SIRI levels did not exhibit a normal distribution. Therefore, for its comparisons among more than two groups, the Kruskall Wallis H test (post-hoc: Dunn test) was used. Categorical variables were given as numbers and percentages, and inter-group comparisons were conducted with the Chi-square and Fisher exact tests. Spearman correlation analyses were applied to evaluate the relationships between the numerical variables. A Spearman correlation coefficient of <0.10 was evaluated as a negligible correlation, 0.10-0.39 as a weak correlation, 0.40-0.69 as a moderate correlation, 0.70-0.89 as a strong correlation, and 0.90-1.00 as an almost perfect very strong correlation.[26] Multivariable logistic regression analysis with the backward Wald method was subsequently performed to identify any possible independent predictors of PPROM. The receiver operating characteristic (ROC) curve analysis was applied to assess diagnostic performance. Threshold values were determined using the Youden index. Comparison of the area under the curves (AUC) was performed with a nonparametric approach using the theory on generalized U-statistics to generate an estimated covariance matrix, as previously reported by DeLong et al.[27] Significance was accepted at p<0.05 (*) for all of the statistical analyses.

## RESULTS

The distribution of age, gravida, parity, abortion history, and previous birth history was similar between the PPROM and the control groups. The mean gestational age at diagnosis for the PPROM group was 30.1±3.7 weeks, the median latent period was 8 days, and the rate of the amnisure test was 24.3%. In the women with PPROM, oligohydramnios was detected in 30% and anhydramnios in 20%. Their basic characteristics are shown in Table 1.

**Table 1.** Demographic and clinical characteristics of the patients.

| Variables | Control group n=70 | PPROM group n=70 | p |
|---|---|---|---|
| Age, years | 27.9±5.3 | 28.3±6.1 | 0.679 |
| Gravida | 3 (2-4) | 3 (2-4) | 0.905 |
| Parity | 1 (0-1) | 1 (0-2) | 0.715 |
| Abortus | 0 (0-1) | 0 (0-1) | 0.986 |
| Previous birth history, n (%) | | | 0.407 |
| No | 27 (38.6) | 22 (31.4) | |
| Vaginal delivery | 24 (34.3) | 32 (45.7) | |
| Caesarean section | 19 (27.1) | 16 (22.9) | - |
| Gestational age at diagnosis, week | - | 30.1±3.7 | - |
| Latent period, days | - | 8 (4-18) | |
| Cervical dilatation, n (%) | | | <0.001* |
| Yes | - | 39 (55.7) | |
| No | 70 (100) | 31 (44.3) | - |
| Amnisure test, n (%) | - | 17 (24.3) | |
| Amniotic fluid index, n (%) | | | <0.001* |
| Normal | 70 (100) | 35 (50.0) | |
| Oligohydramnios | - | 21 (30.0) | |
| Anhydramnios | - | 14 (20.0) | |
| Fetal gender, n (%) | | | 0.854 |
| Female | 20 (28.6) | 22 (31.4) | |
| Male | 50 (71.4) | 48 (68.6) | |

Data are shown as mean ±SD or median (25th-75th quartile) or number and percentage (%). Abbreviations: PPROM, preterm premature rupture of membranes.

The mean hemoglobin level, mean leukocyte count, mean platelets count, mean neutrophil count, and mean monocytes count, and the median CRP level were higher in the PPROM group compared to the control group, while the median leukocyte count was lower. The median NLR (4.8 vs. 3.5, p<0.001), median PLR (145.1 vs. 126.5, p<0.001), median SII (1208.6 vs. 807.4, p<0.001), and median SIRI (3.1 vs. 2.0, p<0.001) were higher in the PPROM group compared to the control group (Table 2).

**Table 2.** Comparison of the laboratory findings between the control and preterm premature rupture of membranes groups.

| Variables | Control group n=70 | PPROM group n=70 | p |
|---|---|---|---|
| Hemoglobin, g/dl | 10.7±1.1 | 11.3±1.6 | 0.006* |
| Leukocytes, $\times10^3$/µl | 9.0±2.0 | 11.9±3.3 | <0.001* |
| Platelets, $\times10^3$/µl | 233.4±64.4 | 252.2±71.2 | 0.103 |
| Neutrophils, $\times10^3$/µl | 6.5±1.4 | 8.2±1.5 | <0.001* |
| Lymphocytes, $\times10^3$/µl | 1.9 (1.6-2.1) | 1.7 (1.5-1.9) | 0.042* |
| Monocytes, $\times10^3$/µl | 0.6±0.2 | 0.7±0.3 | <0.001* |
| NLR | 3.5 (3-4) | 4.8 (3.9-5.9) | <0.001* |
| PLR | 126.5 (108.5-145.2) | 145.1 (117.3-180.8) | 0.001* |
| SII | 807.4 (636.7-956) | 1208.6 (852.9-1524.1) | <0.001* |
| SIRI | 2.0 (1.6-2.5) | 3.1 (2.4-4.3) | <0.001* |
| PDW, % | 15.5±2.7 | 17.2±2.9 | <0.001* |
| RDW, % | 14.4±2.2 | 14.9±1.8 | 0.158 |
| MCV, fL | 87.9±6.3 | 89.6±7.8 | 0.173 |
| MPV, fL | 8.8±1.0 | 9.0±0.8 | 0.170 |
| CRP, mg/L | 1 (0.2-3.1) | 8 (3.1-24.0) | <0.001* |

Data are shown as mean ±SD or median (25th-75th quartile) or number and percentage (%). Abbreviations: CRP, C-reactive protein; MCV, mean corpuscular volume; MPV, mean platelet volume; NLR, neutrophil-to-lymphocyte ratio; PDW, platelet distribution width; PLR, platelet-to-lymphocyte ratio; PPROM, preterm premature rupture of membranes; RDW, red cell distribution width; SII, systemic immune inflammation index; SIRI, systemic inflammation response index.

Among the potential confounding factors associated with PPROM, hemoglobin, SII, SIRI, platelet distribution width (PDW), and CRP were included in the multivariable logistic regression model. Leukocytes or their subtypes, NLR, and PLR were not included in the multivariable regression model because they caused multicollinearity with the SII and SIRI values. Increased SIRI and CRP levels were determined as independent predictors of PPROM. Accordingly, a 1% increase in the SIRI index increased the risk of PPROM by 7.05-fold (OR=7.05, p=0.010) (Table 3). The threshold value of the SIRI was found to be >2.7 with 81.2% sensitivity and 79.1% specificity (AUC=0.854, p<0.001). The SIRI showed superior diagnostic performance compared to the SII in predicting PPROM (Figure 1A).

**Table 3.** Independent predictors of preterm premature rupture of membranes.

| Variables | Univariable regression analysis | | | Multivariable regression analysis | | | VIF |
|---|---|---|---|---|---|---|---|
| | OR | 95% CI | p | OR | 95% CI | p | |
| Hemoglobin | 1.41 | 1.09-1.82 | 0.008* | - | - | - | 1.06 |
| SII | 1.04 | 1.02-1.06 | <0.001* | - | - | - | 1.56 |
| SIRI | 4.6 | 2.60-8.03 | <0.001* | 7.05 | 1.69-57.22 | 0.010* | 1.86 |
| PDW | 1.25 | 1.10-1.43 | 0.001* | - | - | - | 1.14 |
| CRP | 2.76 | 1.34-5.24 | <0.001* | 1.96 | 1.09-23.11 | 0.037* | 1.54 |

CI, confidence interval; CRP, C-reactive protein; OR, odds ratio; PDW, platelet distribution width; SII, systemic immune inflammation index; SIRI, systemic inflammation response index; VIF, variable important factor.

The mean week of delivery, rates of caesarean section, and NICU admission were higher in the PPROM group compared to the control group. The neonatal outcomes of the PPROM group are presented in detail in Table 4. In the PPROM group, there was a moderate negative correlation between the SIRI and the week of delivery (r=-0.492, p<0.001). In PPROM group, SIRI was higher in the presence with complications compared to without complications (3.4 vs. 2.5, p<0.001). In the women with PPROM who developed complications of fetal distress and placental abruption, the median SIRI values were similar However, the median SIRI value in these complication groups was higher compared to the women with PPROM who developed chorioamnionitis complications (Fetal distress: 4.0 vs. Placental abruption: 3.7, vs. Chorioamnionitis: 2.8, p<0.05). In the women with PPROM who developed chorioamnionitis complications, the median SIRI value was similar to those with PPROM without complications (2.8 vs. 2.5, p > 0.05). No significant association was found between the SIRI values and other neonatal outcomes (Table 5). The threshold value of the SIRI in predicting the combined complications of PPROM was >3.2 with 74.8% sensitivity and 76.4% specificity (AUC=0.781, p<0.001). The SIRI showed superior diagnostic performance compared to the SII in predicting the combined complications of PPROM (Figure 1B).

**Table 4.** Neonatal outcomes of the control and preterm premature rupture of membranes group.

| Variables | Control group n=70 | PPROM group n=70 | p |
|---|---|---|---|
| Week of delivery | 39.4±1.2 | 31.0±2.7 | <0.001* |
| Mode of delivery, n (%) | | | 0.037* |
| Vaginal delivery | 33 (47.1) | 21 (30.0) | |
| Caesarean section | 37 (52.9) | 49 (70.0) | |
| Prematurity, n (%) | | | - |
| Extreme preterm | - | 19 (27.1) | |
| Very preterm | - | 22 (31.4) | |
| Moderate preterm | - | 11 (15.7) | |
| Late preterm | - | 18 (25.7) | |
| Birth weight, g | 3387.8±383.4 | 1718.1±619.3 | <0.001* |
| Extremely low | - | 13 (18.6) | |
| Very low | - | 12 (17.1) | |
| Low | - | 38 (54.3) | |
| Normal | 70 (100) | 7 (10.0) | |
| Complication, n (%) | | | <0.001* |
| None | 70 (100) | 45 (64.3) | |
| Fetal distress | - | 13 (18.6) | |
| Placental abruption | - | 8 (11.4) | |
| Chorioamnionitis | - | 4 (5.7) | |
| Neonatal outcome, n (%) | | | <0.001* |
| No need for NICU | 60 (85.7) | 20 (28.6) | |
| NICU admission | 10 (14.3) | 40 (57.1) | |
| Mortality | - | 2 (2.9) | |
| Duration of NICU stay, days | 7 (5-9) | 13 (10-16) | <0.001* |

Data are shown as mean ±SD or median (25th-75th quartile) or number and percentage (%). NICU, neonatal intensive care unit; PPROM, preterm premature rupture of membranes.

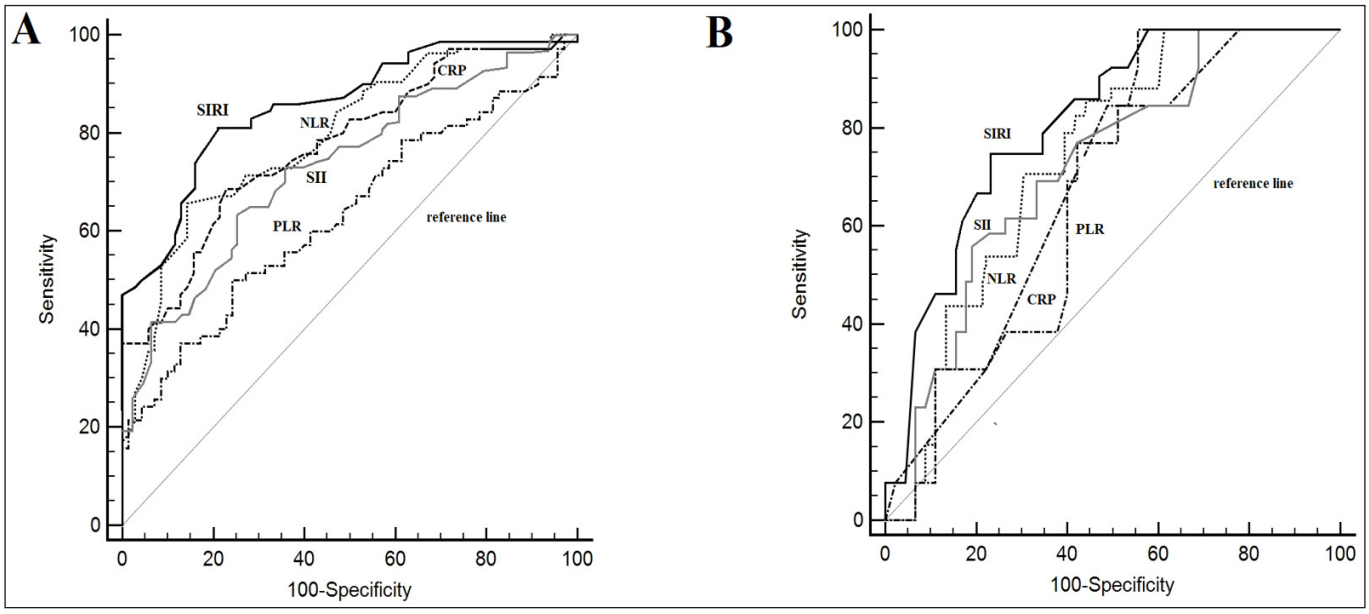


**Figure 1.** Diagnostic performance assessment of the leukocyte-based inflammatory indices in predicting the presence (A) and combined complications (B) of preterm premature rupture of membranes.

**Table 5.** Relationship between the SIRI and neonatal outcomes in the preterm premature rupture of membranes group

| Variables | Median (IQR) or correlation coefficient (r) | p |
|---|---|---|
| Week of delivery | r=-0.492 | <0.001* |
| Mode of delivery | | 0.460 |
| Vaginal delivery | 3.6 (2.4-4.3) | |
| Caesarean section | 3.0 (2.4-4.3) | |
| Prematurity | | 0.598 |
| Extreme preterm | 3.6 (2.9-5.2) | |
| Very preterm | 3.1 (2.3-4.2) | |
| Moderate preterm | 3.0 (2.4-4.3) | |
| Late preterm | 3.7 (2.3-4.5) | |
| Birth weight | - | 0.755 |
| Extreme | 3.7 (2.9-5.2) | |
| Very low | 3.0 (2.6-4.3) | |
| Low | 3.1 (2.3-4.2) | |
| Normal | 3.6 (1.6-4.5) | |
| Complication | | 0.031* |
| None | 2.5 (2.1-3.0) | |
| Fetal distress | 3.7 (2.8-4.5) | |
| Placental abruption | 4.0 (3.5-5.1) | |
| Chorioamnionitis | 2.8 (2.2-3.3) | |
| Neonatal outcome | | 0.582 |
| No need for NICU | 3.5 (2.7-4.2) | |
| NICU admission | 3.0 (2.3-4.7) | |
| Mortality | 4.7 (3.1-6.3) | |

IQR, 25th-75th quartiles; NICU, neonatal intensive care unit; PPROM, preterm premature rupture of membranes.

## DISCUSSION

To the best of our knowledge, this study is the first in the current literature to highlight the association between old and new leukocyte-based inflammatory indices with PPROM and adverse pregnancy outcomes. The levels of SII and SIRI indices were higher in the PPROM group compared to the control group. The SIRI was identified as an independent predictor of PPROM, demonstrating better diagnostic capabilities than other leukocyte-based inflammatory indices. The women with PPROM who developed complications of fetal distress and placental abruption had higher SIRI levels.

The maternal innate immune system plays a significant role in all stages of human pregnancy, including the integrity of the amniotic membrane and the labor process.[28] As gestation progresses, the fetal membranes experience a systematic collagen degradation process, adapting to the rising uterine pressure and expanding volume. The regulation of the collagenolytic process is facilitated by MMPs.[29] During preterm labor, leukocytes, especially neutrophils, from the human decidua produce multiple inflammatory substances and MMPs that disintegrate the extracellular matrix of the fetal membranes.[7] In cases of PPROM, heightened collagenolysis, reduced membrane collagen content, and increased MMPs activation have been documented.[30] On the other hand, various epidemiological and clinical factors, including maternal reproductive system infections, habits like substance abuse, smoking, and inadequate nutritional status, along with pregnancy-related challenges such as gestational bleeding, multiple gestation, and antenatal trauma, may exacerbate to inflammation and elevate the risk of PPROM.[31,32] Therefore, in this study, we omitted patients with additional risk factors to assess the impact of inflammation on PPROM more objectively.

In the PPROM group, there was a notable difference in the levels of neutrophils, lymphocytes, and monocytes among the leukocyte subtypes when compared to the

control group. Among the potential mechanisms involved in the pathogenesis of PPROM is the inflammatory response caused by redox changes. These changes lead to the release of ROS, cytokines, and MMPs, activating the immune system and resulting in neutrophil and macrophage infiltration in the fetal membranes.[7] This is also supported by high leukocyte levels shown in previous PPROM studies.[33-35] Therefore, there has been growing interest in indices derived from complete blood counts, which can be easily and inexpensively obtained in every hospital, for predicting PPROM.

Consistent with current findings, many studies have shown that the NLR is higher in the PPROM group, while there have been conflicting results regarding the PLR .[13,14,36,37] The conflicting results associated with the PLR are attributed to the PLR not changing in cases of oligohydramnios and with normal amniotic fluid volume.[13] In predicting PPROM, the diagnostic performance of the NLR varies between 70%-84% sensitivity and 58%-90% specificity,[13,38] while the diagnostic performance of the PLR ranges between 58%-63% sensitivity and 63%-74% specificity.[39,40] To the best of our knowledge, this was the first study evaluating the diagnostic performance of the SII and SIRI values in distinguishing PPROM. In the PPROM patients, the SII and SIRI values were higher. On the other hand, some inflammatory mechanisms might have contributed to identifying only CRP and SIRI as independent predictors for PPROM. While elevated levels of CRP in circulation can influence leukocyte function through the activation of the complement system,[41] neutrophils and macrophages are involved in the activation and regulation of platelets.[42] It has been shown that platelet indices such as PDW and plateletcrit exhibit a low diagnostic performance in PPROM.[43] This is also consistent with the conflicting results of platelet or PLR in the current literature.[13,14,36,37] All of these findings suggest that neutrophil-macrophage activation may be more dominant in the inflammatory response that plays a role in the pathogenesis of PPROM. Consistent with this, in distinguishing PPROM, the SIRI demonstrated superior diagnostic performance compared to other leukocyte-based inflammatory indices. Therefore, the superior diagnostic performance of the SIRI can be attributed to the activation of neutrophils and macrophages involved in the pathogenesis of PPROM.[7]

In PPROM, which complicates approximately 3% of pregnancies, maternal inflammation plays a significant role in neonatal outcomes.[44] Due to inflammation, the fetus suffers damage and can experience severe complications during the neonatal period, including intraventricular hemorrhage, respiratory distress, and even neonatal compromise.[45] The SIRI was notably linked to adverse neonatal outcomes, particularly fetal distress, and placental abruption. Fetal distress and placental abruption are urgent obstetric situations that necessitate immediate delivery. They often result in a grim prognosis for newborns due to the lack of time for antenatal corticosteroid administration, leaving preterm infants vulnerable to complications associated with prematurity. Previous studies have shown that SII, as well as the NLR and PLR, are significant predictors for forecasting sepsis or adverse neonatal outcomes in PPROM.[14,39,46] However, the SIRI was more successful in predicting composite complications than SII, the NLR, and PLR. Therefore, the SIRI, which encompasses a more comprehensive set of immune cells, could be a significant screening tool in predicting PPROM and adverse neonatal outcomes.

This study had certain limitations. Firstly, due to its retrospective nature, cytokines and chemokines that play a role in PPROM could not be assessed. Additionally, evaluating leukocyte subtypes with flow cytometry analysis might be more elucidative in the development of PPROM. Assessing these factors in large-scale prospective studies could further clarify the role of inflammation indices in PPROM cases.

## CONCLUSION

The PPROM group had higher leukocyte-based inflammation indices compared to the control group. Notably, the SIRI demonstrated superior diagnostic performance in distinguishing both PPROM and combined complications compared to other leukocyte-based inflammation indices. In PPROM, composite indices encompassing a broader range of immune cells may serve as more significant screening tools.

## ETHICAL DECLARATIONS

**Ethics Committee Approval:** The study was carried out with the permission of Kocaeli Derince Training and Reseach Hospital Clinical Researches Ethics Committee (Date: 12.01.2023, Decision No: 2023-001).

**Informed Consent:** Because the study was designed retrospectively, no written informed consent form was obtained from patients.

**Referee Evaluation Process:** Externally peer-reviewed.

**Conflict of Interest Statement:** The authors have no conflicts of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

**Author Contributions:** All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

## REFERENCES


1. Committee on Practice B-O. ACOG practice bulletin no. 188: Prelabor Rupture of Membranes. *Obstet Gynecol.* 2018;131(1):e1-e14. doi: 10.1097/AOG.0000000000002455
2. Garg A, Jaiswal A. Evaluation and management of premature rupture of membranes: a review article. *Cureus.* 2023;15(3):e36615. doi: 10.7759/cureus.36615
3. Kenyon S, Boulvain M, Neilson JP. Antibiotics for preterm rupture of membranes. *Cochrane Database Syst Rev.* 2010(8):CD001058. doi: 10.1002/14651858.CD001058.pub2
4. Galaz J, Romero R, Slutsky R, et al. Cellular immune responses in amniotic fluid of women with preterm prelabor rupture of membranes. *J Perinat Med.* 2020;48(3):222-233. doi: 10.1515/jpm-2019-0395
5. Romero R, Miranda J, Chaemsaithong P, et al. Sterile and microbial-associated intra-amniotic inflammation in preterm prelabor rupture of membranes. *J Matern Fetal Neonatal Med.* 2015;28(12):1394-1409. doi: 10.3109/14767058.2014.958463
6. Polettini J, Silva MG, Kacerovsky M, Syed TA, Saade GR, Menon R. Screening of lysyl oxidase (LOX) and lysyl oxidase like (LOXL) enzyme expression and activity in preterm prelabor rupture of fetal membranes. *J Perinat Med.* 2016;44(1):99-109. doi: 10.1515/jpm-2014-0337
7. Menon R, Behnia F, Polettini J, Richardson LS. Novel pathways of inflammation in human fetal membranes associated with preterm birth and preterm pre-labor rupture of the membranes. *Semin Immunopathol.* 2020;42(4):431-450. doi: 10.1007/s00281-020-00808-x
8. Musilova I, Kutova R, Pliskova L, et al. Intraamniotic inflammation in women with preterm prelabor rupture of membranes. *PLoS One.* 2015;10(7):e0133929. doi: 10.1371/journal.pone.0133929
9. Rosales C. Neutrophil: a cell with many roles in inflammation or several cell types? *Front Physiol.* 2018;9:113. doi: 10.3389/fphys.2018.00113
10. Etyang AK, Omuse G, Mukaindo AM, Temmerman M. Maternal inflammatory markers for chorioamnionitis in preterm prelabour rupture of membranes: a systematic review and meta-analysis of diagnostic test accuracy studies. *Syst Rev.* 2020;9(1):141. doi: 10.1186/s13643-020-01389-4
11. Le Ray I, Mace G, Sediki M, et al. Changes in maternal blood inflammatory markers as a predictor of chorioamnionitis: a prospective multicenter study. *Am J Reprod Immunol.* 2015;73(1):79-90. doi: 10.1111/aji.12323
12. Back JH, Kim SY, Gu MB, et al. Proteomic analysis of plasma to identify novel biomarkers for intra-amniotic infection and/or inflammation in preterm premature rupture of membranes. *Sci Rep.* 2023;13(1):5658. doi: 10.1038/s41598-023-32884-y.
13. Esercan A, Demir I. Neutrophil/lymphocyte and platelet/lymphocyte ratio in preterm premature rupture of membranes. *Cureus.* 2023;15(5):e38664. doi: 10.7759/cureus.38664
14. Ozel A, Alici Davutoglu E, Yurtkal A, Madazli R. How do platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio change in women with preterm premature rupture of membranes, and threaten preterm labour? *J Obstet Gynaecol.* 2020;40(2):195-199. doi: 10.1080/01443615.2019.1621807
15. Bodaghi A, Fattahi N, Ramazani A. Biomarkers: Promising and valuable tools towards diagnosis, prognosis and treatment of Covid-19 and other diseases. *Heliyon.* 2023;9(2):e13323. doi: 10.1016/j.heliyon.2023.e13323
16. Indrayan A, Vishwakarma G, Verma S, Sarmukaddam S, Tyagi A. Quest for biomarkers of positive health: a review. *Indian J Community Med.* 2023;48(3):382-389. doi: 10.4103/ijcm.ijcm_480_22
17. Gunduz O, Seven B, Ozgu-Erdinc AS, et al. Correlation of systemic inflammation biomarkers and disease severity in pregnant women with COVID-19. *Rev Assoc Med Bras (1992).* 2023;69(6):e20221614. doi: 10.1590/1806-9282.20221614
18. Lombardi A, Duiella S, Li Piani L, et al. Inflammatory biomarkers in pregnant women with COVID-19: a retrospective cohort study. *Sci Rep.* 2021;11(1):13350. doi: 10.1038/s41598-021-92885-7
19. Hu B, Yang XR, Xu Y, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. *Clin Cancer Res.* 2014;20(23):6212-6222. doi: 10.1158/1078-0432.CCR-14-0442
20. Qi Q, Zhuang L, Shen Y, et al. A novel systemic inflammation response index (SIRI) for predicting the survival of patients with pancreatic cancer after chemotherapy. *Cancer.* 2016;122(14):2158-2167. doi: 10.1002/cncr.30057
21. Yun S, Yi HJ, Lee DH, Sung JH. Systemic inflammation response index and systemic immune-inflammation index for predicting the prognosis of patients with aneurysmal subarachnoid hemorrhage. *J Stroke Cerebrovasc Dis.* 2021;30(8):105861. doi: 10.1016/j.jstrokecerebrovasdis.2021.105861
22. Li J, He D, Yu J, et al. Dynamic status of SII and SIRI alters the risk of cardiovascular diseases: evidence from kailuan cohort study. *J Inflamm Res.* 2022;15:5945-5957. doi: 10.2147/JIR.S378309
23. Krawczyk P, Sioma-Markowska U. Nutrition quality of pregnant women based on body mass index and the content of selected nutrients and energy in the daily diet. *Ginekol Pol.* 2021. doi: 10.5603/GP.a2021.0069
24. Committee on Practice B-O. ACOG Practice Bulletin No. 199: Use of prophylactic antibiotics in labor and delivery. *Obstet Gynecol.* 2018;132(3):e103-e119. doi: 10.1097/AOG.0000000000002833
25. Quinn JA, Munoz FM, Gonik B, et al. Preterm birth: Case definition & guidelines for data collection, analysis, and presentation of immunisation safety data. *Vaccine.* 2016;34(49):6047-6056. doi: 10.1016/j.vaccine.2016.03.045
26. Schober P, Boer C, Schwarte LA. Correlation coefficients: appropriate use and interpretation. *Anesth Analg.* 2018;126(5):1763-1768. doi: 10.1213/ANE.0000000000002864
27. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics.* 1988;44(3):837-845.
28. Areia AL, Moura P, Mota-Pinto A, CRD PNm. The role of innate immunity in spontaneous preterm labor: A systematic review. *J Reprod Immunol.* 2019;136:102616. doi: 10.1016/j.jri.2019.102616
29. Menon R, Fortunato SJ. Infection and the role of inflammation in preterm premature rupture of the membranes. *Best Pract Res Clin Obstet Gynaecol.* 2007;21(3):467-478. doi: 10.1016/j.bpobgyn.2007.01.008
30. Vadillo-Ortega F, Estrada-Gutierrez G. Role of matrix metalloproteinases in preterm labour. *BJOG.* 2005;112 Suppl 1:19-22. doi: 10.1111/j.1471-0528.2005.00579.x
31. Bouvier D, Forest JC, Blanchon L, et al. Risk factors and outcomes of preterm premature rupture of membranes in a cohort of 6968 pregnant women prospectively recruited. *J Clin Med.* 2019;8(11):1987. doi: 10.3390/jcm8111987
32. Jena BH, Biks GA, Gete YK, Gelaye KA. Incidence of preterm premature rupture of membranes and its association with inter-pregnancy interval: a prospective cohort study. *Sci Rep.* 2022;12(1):5714. doi: 10.1038/s41598-022-09743-3
33. Musilova I, Pliskova L, Gerychova R, et al. Maternal white blood cell count cannot identify the presence of microbial invasion of the amniotic cavity or intra-amniotic inflammation in women with preterm prelabor rupture of membranes. *PLoS One.* 2017;12(12):e0189394. doi: 10.1371/journal.pone.0189394
34. Yoon BH, Jun JK, Park KH, Syn HC, Gomez R, Romero R. Serum C-reactive protein, white blood cell count, and amniotic fluid white blood cell count in women with preterm premature rupture of membranes. *Obstet Gynecol.* 1996;88(6):1034-1040. doi: 10.1016/s0029-7844(96)00339-0

35. Eriç Horasanlı J, Alp EC, Bülbül R. Evaluation of complete blood cell count parameters in the diagnosis of threatened preterm labor and premature rupture of membranes. *Dubai Med J.* 2022;5(3):157-162.

36. Koseoglu SB, Guzel AI, Deveer R, et al. Maternal serum amyloid A levels in pregnancies complicated with preterm prelabour rupture of membranes. *Ginekol Pol.* 2014;85(7):516-520. doi: 10.17772/gp/1763

37. Ekin A, Gezer C, Kulhan G, Avci ME, Taner CE. Can platelet count and mean platelet volume during the first trimester of pregnancy predict preterm premature rupture of membranes? *J Obstet Gynaecol Res.* 2015;41(1):23-28. doi: 10.1111/jog.12484

38. Uckan K, Baskiran Y, Celegen I. Association of subclinical markers of inflammation with preterm premature rupture of membranes and adverse neonatal results: a case control study. *Arch Gynecol Obstet.* 2022;306(6):2063-2068. doi: 10.1007/s00404-022-06756-1

39. Toprak E, Bozkurt M, Dincgez Cakmak B, et al. Platelet-to-lymphocyte ratio: A new inflammatory marker for the diagnosis of preterm premature rupture of membranes. *J Turk Ger Gynecol Assoc*. 2017;18(3):122-126. doi: 10.4274/jtgga.2017.0028

40. Sharami SH, Biazar G, Farzi F, et al. The association between platelets/lymphocyte ratio and premature rupture of membranes. *Int J Women's Health Reprod Sci.* 2021;9(1):80-83.

41. Badimon L, Pena E, Arderiu G, et al. C-reactive protein in atherothrombosis and angiogenesis. *Front Immunol.* 2018;9:430. doi: 10.3389/fimmu.2018.00430

42. Su Y, Gao J, Kaur P, Wang Z. Neutrophils and macrophages as targets for development of nanotherapeutics in inflammatory diseases. *Pharmaceutics.* 2020;12(12):1222. doi: 10.3390/pharmaceutics12121222

43. Dundar B, Dincgez Cakmak B, Ozgen G, Tasgoz FN, Guclu T, Ocakoglu G. Platelet indices in preterm premature rupture of membranes and their relation with adverse neonatal outcomes. *J Obstet Gynaecol Res.* 2018;44(1):67-73. doi: 10.1111/jog.13484

44. Mercer BM. Preterm premature rupture of the membranes. *Obstet Gynecol.* 2003;101(1):178-193. doi: 10.1016/s0029-7844(02)02366-9

45. Xie A, Zhang W, Chen M, et al. Related factors and adverse neonatal outcomes in women with preterm premature rupture of membranes complicated by histologic chorioamnionitis. *Med Sci Monit.* 2015;21:390-395. doi: 10.12659/MSM.891203

46. Tanacan A, Uyanik E, Unal C, Beksac MS. A cut-off value for systemic immune-inflammation index in the prediction of adverse neonatal outcomes in preterm premature rupture of the membranes. *J Obstet Gynaecol Res.* 2020;46(8):1333-1341. doi: 10.1111/jog.14320